Old Drugs, New Therapies

By Dr Roberto Castangia at Biopharma Group

In order to successfully achieve innovation in the R&D process across the pharmaceutical sector, experts are calling for a fresh approach to drug development techniques. It is now possible that drug repositioning could revolutionise medicine

Innovative technologies often rely on a response to market demands and imply a sustainable strategy for economic growth. In this regard, the increasing demand for new medications makes the pharmaceutical industry one of the most complex sectors of today (see Figure 1).

Drug Development in Numbers

According to EvaluatePharma (2), worldwide prescription drug sales counted from 2014 are expected to reach almost one trillion dollars by 2020, with a compound annual growth rate (CAGR) of 4.8%.

This economic success is attributed to the ability to offer the most reliable benefits to society and improve overall public health in terms of life expectancy, quality of life and more affordable medical assistance.

With its impact on human health, drug development (DD) has directly contributed to extending life expectation by almost 15 years when compared to the mid-20th century. This success has, however, come at a price. Resources for R&D require strict control to sustain long-term investments and tackle problems such as patent expiration. In addition, new drugs demand a high level of originality, efficacy and safety when compared to existing over-the-counter (OTC) or generic equivalents (see Figure 2, page 8).

From a different perspective, a new product requires a high level of accuracy in the prediction of market response throughout its lifecycle, from concept through development, into commercialisation until withdrawal from the market. Product lifecycle management (PLM) has become of critical importance to ensure business sustainability and profitability.

Many models have been adopted in the optimisation of PLM, while new approaches to R&D are regularly examined (4) –

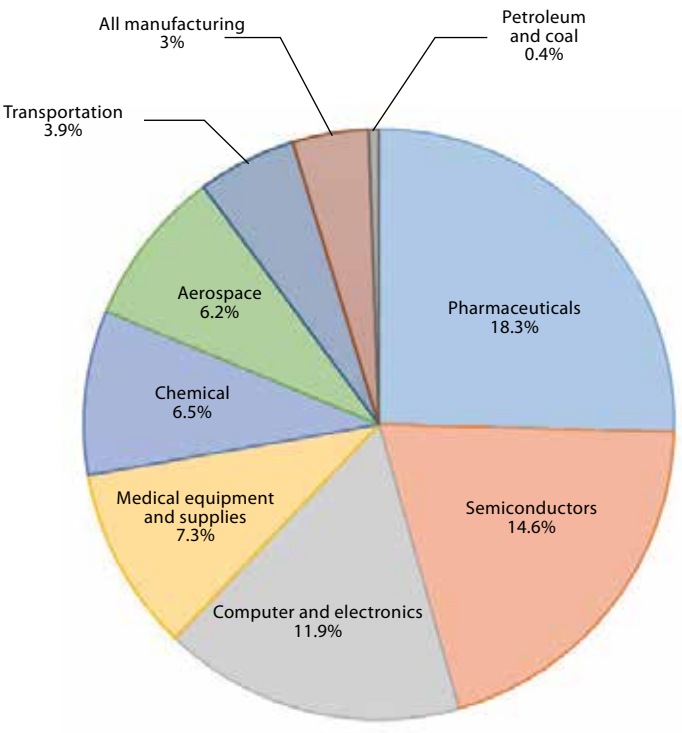

Figure 1: Distribution of R&D investments – total sales in different industrial sectors

Source: Adapted from PhARMA, 2015 (1)

Keywords

Innovative technology
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Formulation and reformulation
Nanotechnology

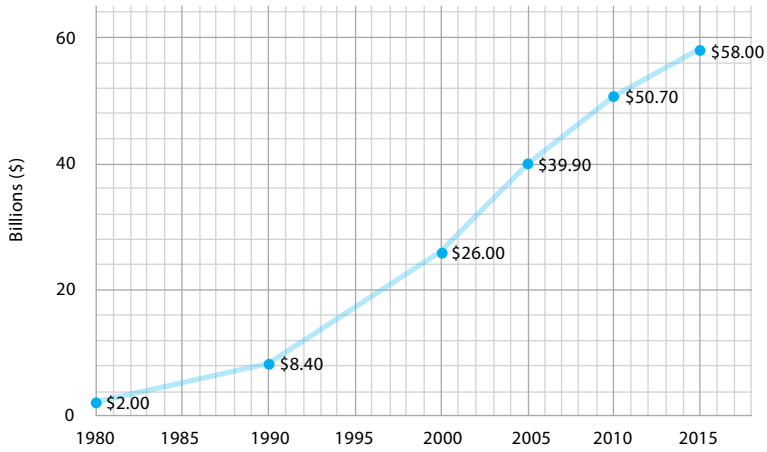

Figure 2: R&D investments in the pharmaceutical sector over 35 years

Source: Adapted from US FDA Novel drugs 2015, January 2016 summary (3)

the reasoning being that pharma firms are forced to spend more and more on DD costs, which are then reflected in higher end user pricing (5).

As shown in Figure 3, the capitalised cost for a drug throughout its development has been estimated around $2.5 billion, 90% of which is cost-sustained for R&D in the pre-approval stage. When compared to development expenses 10 years ago, the figure is now 2.5 times higher (6).

Trends account for investments that have to be sustained over a span of more than 20 years, assuming the new molecular entity (NME) is approved by regulatory agencies and reaches the market.

In order to mitigate development costs, many companies have cut the number of R&D personnel or have outsourced projects to service providers, mainly located in cheaper countries. As a result, this has supplied demand for CROs and contract manufacturing organisations in emerging markets, which have been growing exponentially for the last 10 years (7).

For example, in 2015, the FDA approved 45 new drugs over a precedent average of 28. It is worth noting that 16 out of the 45 new drugs were approved as first-in-class, meaning that they have a different mechanism of action from those of the same kind (see Figure 4, page 10).

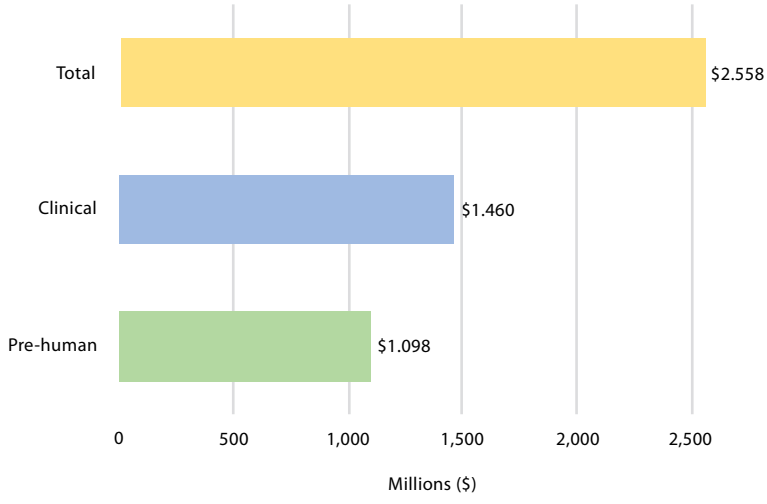

Figure 3: Estimated capital cost in NME development

Source: Adapted from DiMasi et al, *2016*

The significance of these figures is that their origins are in new technologies such as combinatorial chemistry, high-throughput screenings and new analytical devices. Moreover, advances in computational chemistry, genomics, and molecular and cellular biology have provided great opportunities and opened up new challenges. For example, progress in molecular biology has given access to therapeutic targets on well-characterised structures and functions, unveiling details not previously fully understood.

Formulation to Reformulation

In a scenario of pharma and biotech companies rushing for NMEs, a parallel method has been embraced to approach the development from a completely different perspective. This is the case in modified dosage forms and generic formulations development. In the last decade, it has been attracting primary attention as it relies on a reformulation of approved active pharmaceutical ingredients (APIs) and the optimisation of safety, efficacy and release time. The principle appears simple – but the implications in development cost and time are enormous.

In this instance, discovery and screening – the most expensive and time-demanding phases in a de novo process – are bypassed, ensuring a quicker route to market. In addition, the regulatory approval for commercialisation is less cumbersome and can often be obtained – avoiding long, expensive clinical trials.

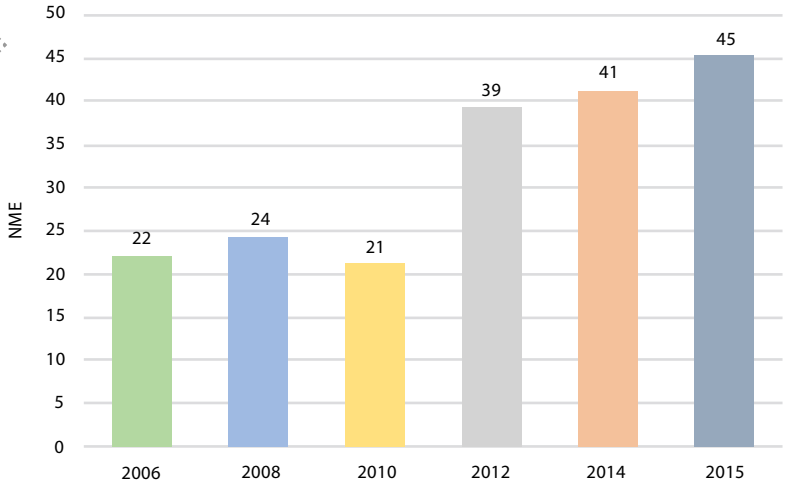

Figure 4: NMEs biannually approved by the FDA

Source: Adapted from US FDA, Novel drugs 2015, January 2016 summary

In practical terms, development time for a reformulated API can be shortened to between four and 10 years, versus 12 to 20 years typically required in a de novo approach. The idea of using clinically approved APIs goes along with the scope of discovering new actions/applications and applies their activity in treatments that are diverse from their original intent. This specific approach is otherwise known as drug repositioning (8).

Nowadays, there are many instances of repositioned drugs that have found successful applications in new therapies – one well-known example being aspirin. The German company Bayer developed it in 1897 as an anti-inflammatory and painkiller, but now it is also used as an antiplatelet drug for treating and preventing heart attacks or strokes. Viagra, ibuprofen and Rogaine are also well-known examples of repositioned drugs.

The paradigm shift of new applications for old drugs has unveiled the complexity – as well as amplified the need for – greater understanding of delivery and targeting strategies.

With the advent of nano-technology, newer approaches are being explored for formulation in a submicron size, identifying the new concept of nanoformulation. Drug carriers are designed with surface modifications in charges, affinity groups and functionalised ligands. In this way, nanocarriers define the next generation of medication for high-risk drugs such as anticancer, antiretroviral and neuroleptics. Amongst many forms, solid nanoparticles, liposomes, nanospheres, nanocapsules, dendrimers and polymeric micelles are the most commonly used. As such, targeted delivery, selective permeation and longer circulation time in the bloodstream are successfully accomplished.

Innovation is Multi-Modal

When discussing innovations in the pharmaceutical field, the crucial contribution of complementary disciplines in chemistry and biology should not be neglected. The synergetic approach of informatics, physics and engineering has allowed the integration of the generation, collection and analysis of millions of datasets in a successful manner. In addition, interdisciplinary models are accounting for the remarkable progress in diagnostics and medical devices. For example,

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the field of bioinformatics is playing a crucial role in the development of personalised medicine, supporting biological data analysis in a high-throughput fashion at a speed previously inconceivable.

Data analysis with new and more affordable DNA sequencing techniques are supporting pharmacogenetics and pharmacogenomics in understanding the implications of genes in drug interactions and metabolism. In cancer therapy, for example, tailored dosages can rely on higher efficacy and reduced side effects, increasing overall tolerability and cost efficiencies (9).

New therapies have also taken advantage of the use of immunology, identifying in the immune system an alternative to chemotherapy in the treatment of diseases and ailments. Although known for over a century, immunogenic approaches have only recently become valid alternatives to surgery, radiotherapy and targeted therapy. Immunotherapy relies heavily on agents that target a tumour directly, or agents that activate immune cells that target the tumour in response. The overall range includes monoclonal antibodies, immunotoxins, vaccines and entire cells such as T cells (10).

Looking to the Future

The capital cost for advanced technologies burdens pharma and biotech companies with financial constraints. Where some act as innovators and knowledge creators, experts suggest that a model accounting for internal core competencies, outsourced service providers and cost sustainability should be adopted. For the majority, cutting-edge innovation is unaffordable – however, success can still be guaranteed following models like generics business or drug repositioning, or by targeting emerging markets (7,11).

By definition, innovation refers to a way of making changes in something already established, achieved by introducing new methods, ideas or products. From a social perspective, it should not matter in which way pharma innovation occurs, as long as progress of human health is the core objective within regulation guidelines.

However, in reality, the recent exposure of health threats has provided examples which indicate that human necessity may not be the primary reason for implementing an innovation model.

In light of this, and with the recent upsurge in drug-resistant bacteria together with the ongoing debate as to the cause, the global community has been shaken – revealing the weakness of current technologies and the incapacity to proactively address the reasons for the occurrence of such issues.

It is now second nature to question whether in cases like these, industry innovation is matching the concept of progress (12,13,14). The debate continues.

References
1. PhARMA, Annual 2016 Pharmaceutical Industry Profile, Accessed May 2016. Visit: www.phrma.org/profiles-reports
2. EvaluatePharma World Preview 2015, Outlook to 2020, Accessed May 2016. Visit: www.evaluategroup.com/public/reports/EvaluatePharma-World-Preview-2015.aspx
3. US FDA, Novel drugs 2015, January 2016 summary, Accessed May 2016. Visit: www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM485053.pdf
4. Owens PK *et al, Nature Reviews Drug Discovery* 14, 2015
5. Arnold DG and Troyer JL, *Journal of Health Politics, Policy and Law* 41(2), 2016
6. DiMasi JA *et al, Journal of Health Economics* 47: pp20-33, 2016
7. Schuhmacher A *et al, Journal of Translational Medicine* 14: p105, 2016
8. Ashburn TT and Thor KB, *Nature Reviews Drug Discovery* 3: p673, 2004
9. Berm EJJ *et al*, PLOS ONE, DOI:10.1371/journal.pone.0146262, 11 January 2016
10. Sathyanarayanan V and Neelapu SS, *Molecular Oncology* 9: pp2,043-2,053, 2015
11. Banerjee K and Thakurta R, *Journal of Generic Medicines* 12: pp50-59, 2015
12. Meredith HR, *Nature Chemical Biology* 11, 2015
13. Blair MA *et al, Nature Reviews* 42(13), 2015
14. Berendonk TU *et al, Nature Reviews Microbiology* 310(13), 2015

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